Section of Odontology

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President's Address

Changing Views on Oral Disease

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In this paper comment will be made on some of the changes that have taken place in our views about various mouth and jaw lesions during the past 25 years. It is clearly not possible to attempt any comprehensive coverage: and I should also emphasize that all my comments are from the viewpoint of a diagnostic pathologist. There will therefore be no reference to advancing knowledge and changing views in the important areas of caries and periodontal diseases as these are areas in which the diagnostic pathologist can make little contribution.

'White Lesions' of the Oral Mucosa

Long before the period under review, leukoplakia was recognized as a precancerous condition; indeed, a high proportion of leukoplakias progressed to carcinoma. However, most of these were syphilitic leukoplakias, and now that this condition has become rare a whole variety of other white lesions has been identified. In recent years, attention has been focused on the so-called candidal leukoplakias, and on 'speckled leukoplakia' (or speckled erythroplakia), as lesions with a greater predisposition to malignant change than the other white lesions.

Candida albicans is commonly an inhabitant of the normal mouth, but it is an opportunistic pathogen. If there is some local or systemic change in the resistance of the tissue to infection, candida may invade the epithelium and produce white areas. In candidal leukoplakia, the diagnosis can often be suspected from the clinical appearances, because the patches tend to be much whiter and more opaque than other white lesions of the mucosa. There seem to be no statistics from large series of cases, but present evidence suggests that candidal leukoplakia may be about three times more likely to progress to carcinoma than non-candidal leukoplakia (Cawson 1969).

Speckled leukoplakia is characterized by the co-existence of white and red patches, and in many such lesions a candida infection can be demonstrated. It is also well established that the risk of malignant change is substantially greater than in ordinary leukoplakias.

These observations might suggest that chronic candidal infection predisposes to carcinoma. However, other studies suggest that the relationship between candidiasis and carcinoma may be indirect. Lehner and his colleagues (1972) have published evidence that the patient with chronic oral candidiasis may have this infection because of a defect in the natural body defences – a defect in the immunological mechanisms. It is also believed that these mechanisms may provide one of our main lines of defence against malignant neoplasms. It is a widely held view that all of us repeatedly develop cells with malignant characteristics, but on most occasions these altered cells are recognized as altered and foreign by our immunological defences, and are destroyed before clinical neoplasia occurs.

It may be, then, that chronic candidal infection and predisposition to neoplasia are both related to a third factor – an immunological defect, but here we must mention another observation. In areas of candidal infection, the epithelium often shows marked dysplasia or atypia. These changes in the pattern of the epithelium, and in the morphology of the cells, are of the type that often precede carcinoma, but in chronic candidiasis, if the infection can be eliminated, the epithelial dysplasia may disappear at the same time. Does this indicate that candidal infection has a direct

action on the epithelium, producing changes that predispose to carcinoma, or does it indicate that candida-induced epithelial dysplasia is of a type that has no particular significance in relation to future malignancy? We know that in certain other diseases, such as lichen planus, marked epithelial dysplasia may occur without much likelihood of malignant change (Kramer *et al.* 1970*a*).

Most work on precancerous lesions has been done on the cervix, and there are many similarities between the lesions in the cervical and the oral sites. Cervical cancer, and cervical carcinoma-in-situ are common, although it is as well to remember that, in the cervix, carcinoma-in-situ does not necessarily proceed to invasive cancer.

Petersen (1956) described a series of 127 patients in whom carcinoma-in-situ of the cervix had been diagnosed, and these patients were followed over a period of several years without receiving any definitive treatment. Of the 127 patients, 11% showed invasive carcinoma at the end of three years, 22% after five years, and 39% after nine years. In other words, after nine years, 61% of the patients did not show progression to invasive carcinoma.

It would, of course, be most unwise to assume that such a trend would also apply to lesions of the oral mucosa. Carcinoma-in-situ of the mouth is comparatively uncommon, but it is the impression of many of us that, when it does occur, progression to invasive carcinoma is the usual consequence.

A very different form of oral carcinoma has been recognized comparatively recently as a distinctive entity (Ackerman 1948), and that is the verrucous carcinoma. This lesion is perhaps the most highly differentiated and least malignant of all the oral carcinomata. Usually seen in older patients, the lesion is exophytic and grows slowly. For a long time, sometimes for years, it grows in a verrucous or warty pattern, although ultimately it may invade. Surgical treatment is usually simple and the results are very satisfactory, but present evidence suggests that irradiation should be avoided, for this may lead to the development of an invasive tumour.

Whilst on the topic of white patches in the mouth, I should like to refer to changes in opinion regarding a rather distinctive lesion of the floor of the mouth and under surface of the tongue.

The patient with this type of lesion is always an adult, the lesion is usually symmetrical and painless, and the appearance of the affected area tends to vary slightly from week to week. Sometimes parts of it are heaped up and white, sometimes there is a less marked greyness, and commonly there is a rippled appearance.

Within the period that I am reviewing, this floor of the mouth lesion was recognized as a distinctive entity by Cooke (1956), and it has also been suggested that the condition is a non-familial developmental anomaly, somewhat similar to the inherited white sponge nævus of Cannon. If the floor of the mouth lesion is a developmental anomaly, one wonders why it is rarely if ever seen in children (and the same comments apply to the so-called median rhomboid glossitis).

However, many have now seen malignant changes in these floor of the mouth lesions, and I think it wise to regard them as a form of precancerous leukoplakia: whether or not they are developmental in origin, they are certainly not always harmless.

Odontogenic Tumours

In the field of tumour pathology the practical purpose of classification is to identify and separate those lesions that behave in different ways and therefore require different forms of treatment. Frequently, what appear to be wide variations in the structure and behaviour of a single type of tumour are later shown to be due to the confusion of two or more quite different entities.

This process of identification and separation has made remarkable progress in that very complex collection of lesions that arise from the odontogenic tissues, and one group of examples will suffice to illustrate this progress.

Not very long ago most tumours or tumour-like lesions of odontogenic epithelium were classified as ameloblastomas, and there was a variety of subdivisions including 'adenoameloblastoma', 'melanotic ameloblastoma', and a miscellaneous collection of atypical oddments. It was apparent that the ameloblastoma was a locally invasive lesion, and that, if treated by simple curettage, there was a considerable risk of recurrence. Consequently, treatment in certain cases was often more radical than we now consider necessary.

Obviously, the more radical the treatment, the more important it becomes that the lesion should be accurately identified.

It is now generally accepted that the so-called adenoameloblastoma is not a variant of the ameloblastoma: it is a quite separate and distinctive entity. Whilst its microscopic structure provides a happy hunting ground for histologists, histochemists and electron microscopists, we know that it is a very benign, non-infiltrative lesion. Indeed, it is doubtful whether it is a neoplasm at all. It is easily enucleated and recurrence following enucleation is almost unknown. Therefore the adenoameloblastoma, or adenomatoid odontogenic tumour, is treated quite differently from the ameloblastoma.

The so-called melanotic ameloblastoma is also recognized now as a lesion that does not belong to the ameloblastoma group; in fact, in retrospect it is difficult to see why it was ever thought to arise from odontogenic epithelium.

This very distinctive lesion most commonly occurs in the anterior part of the maxilla in a child under 1 year of age. It usually contains two morphologically different cell types: large, pale cells bearing some resemblance to epithelial cells and often laden with melanin, and small rounded cells somewhat resembling lymphocytes. There is good evidence that the lesion arises from cells derived from the neural crest, and it is now recommended that the lesion should be referred to as the melanotic neuroectodermal tumour of infancy. Despite its infiltrative and destructive behaviour it rarely recurs, and its status as a neoplasm remains a matter for debate.

Two further entities have now been sorted out from the miscellany of supposedly atypical lesions. The calcifying epithelial odontogenic tumour of Pindborg has aroused considerable interest, not only because it has been recognized as something quite different from the ameloblastoma but also because of two unusual histological characteristics. The first is the presence within the tumour of globules of a material that appears to be amyloid or some closely related substance. Whilst the presence of amyloid-like material is of considerable theoretical interest, there is another feature of greater practical importance. Many of these tumours show considerable pleomorphism of the tumour cells. Any pathologist who is working from general principles, rather than from a detailed knowledge of this particular type of tumour, will diagnose the lesion as malignant. However, this rather frightening pleomorphism is misleading, for the Pindborg tumour is benign.

Another distinctive entity that we can now recognize is the calcifying odontogenic cyst, and one of its most characteristic features is the presence of masses of so-called ghost epithelial cells, very like those seen in the calcifying epithelioma of Malherbe. In the past, this lesion was usually diagnosed as an 'atypical ameloblastoma', and parts of the lesion may have a pattern that is very like that of an ameloblastoma. However, the calcifying odontogenic cyst is easily enucleated, is unlikely to recur, and may not be a neoplasm at all. Incidentally, although it is called the calcifying odontogenic cyst, not all of them calcify, and not all are cystic.

Cysts

The teaching that I received led me to define a cyst as a pathological cavity, having fluid, semi-fluid or gaseous contents, and not created by the accumulation of pus: this is the definition I have used in my own teaching for many years.

There are other definitions, but the one that really puzzles me is the definition that demands an epithelial lining. I am not sure how, or why, the presence of an epithelial lining became included in the definition: clearly it creates difficulties, because so many lesions that have been accepted for generations as 'legitimate' cysts must now be termed pseudocysts, or false cysts, or 'cysts' in quotation marks.

It is certainly true that most cysts of the mouth and jaws have an epithelial lining, but who decided that we could not call a traumatic bone cyst a cyst, or a mucous extravasation cyst, or an aneurysmal bone cyst, or the various cysts that occur in other bone disorders? I have the impression that the demand for an epithelial lining has quietly appeared and spread without a logical basis.

Most classifications of the epithelial cysts of the jaws make a primary division between those that are odontogenic, usually with subdivisions along the lines shown in Table 1, and those which used to be termed fissural cysts, even if there is some disagreement about the validity of the term fissural.

Table 1

Odontogenic cysts

Gingival
Eruption
Dentigerous
Lateral periodontal (developmental)
Primordial (keratocyst)
Radicular (dental and residual)

Table 2

'Fissural' cysts

Nasolabial
Nasopalatine (incisive canal)
Globulomaxillary
Median palatal
Median mandibular

This particular group (Table 2) includes two entities that seem to be very debatable. It takes a lot of courage, or a childish innocence, to ask about the Emperor's new clothes. May I shelter behind a childish innocence, and ask whether the median palatal cyst really exists as an entity?

Of course, there are cysts in the midline of the palate, but how many of them are not cysts in the incisive canal – nasopalatine cysts. Cysts arising in other sites may extend as far as the midline, but they do not arise there. Is there really such a thing as a median palatal cyst as distinct from a nasopalatine cyst, or a cyst of the palatine papilla? It seems that we need better evidence if

we are to justify the continuing inclusion of median palatal cyst in our classification.

May I also cast doubts on the median mandibular cyst as a separate entity? Of course, one does sometimes see a cyst in the midline of the mandible, but how often is it a distinctive entity, and not a dentigerous, dental or primordial cyst that just happens to be in that location? The World Health Organization publication on the classification of odontogenic tumours, jaw cysts and allied lesions (Pindborg *et al.* 1972) deliberately omits median palatal and median mandibular cysts.

The primordial cyst or odontogenic keratocyst is a comparatively common lesion, forming somewhere between 4% and 11% of all jaw cysts. It has a very distinctive histological appearance and also distinctive clinical features and behaviour. The cyst lining is a very thin stratified squamous epithelium that is keratinizing, and the cyst grows by the accumulation of this keratin (as opposed to most other cysts, which enlarge because of the accumulation of fluid). It seems to me that the shape of the cyst may be related to this mode of enlargement, and it is well known that the odontogenic keratocyst may have an irregular or lobulated outline. Cysts which enlarge by the accumulation of fluid presumably exert an outward pressure that is equal in all directions. However, the keratocyst often contains thick cheesy keratin: if one part of the epithelial lining is producing keratin at a greater rate, this locally increased production of a rather firm material might account for the uneven pushing out of the cyst wall (Fig 1). Toller (1970) has shown that the relatively scanty cyst fluid in the keratocyst has a lower content of soluble protein than other jaw cysts, and this provides a method that may be used for preoperative identification of the keratocyst. So too does examination of the cyst contents for squames, and both these methods can be applied to material aspirated by a needle pushed through the overlying soft tissue and bone (Kramer & Toller 1973).

One of the principal reasons why keratocysts have attracted so much attention is because they have a particular predisposition to recur following enucleation. In many instances recurrence may be dealt with easily, unless the lesion escapes into the soft tissues. If this happens, it may spread so far that it becomes a major surgical problem.

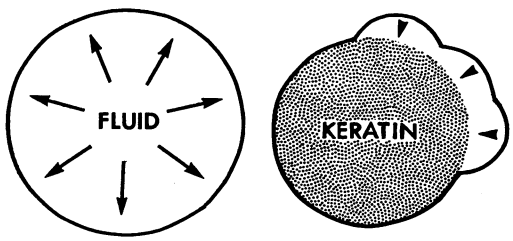

Fig 1 *Diagrams showing growth of fluid-filled cysts (left) and keratocysts (right)*

Why is the keratocyst so much more likely to recur than other jaw cysts? Anyone who has handled the lining of a typical odontogenic keratocyst will know that it is rather like wet cigarette paper: it is very thin and very friable. Also, the epithelium readily separates from the fibrous capsule, and presumably this stripped-off epithelium may be reimplanted into the tissues. Many keratocysts have adjacent microcysts, or islands of epithelium that are separate from the main lining, and often it must be almost impossible to ensure that these have been removed. Furthermore the epithelium of the keratocyst is very active, having a much higher mitotic rate than most other linings (Main 1970, Toller 1971), and consequently any epithelium that is left behind is likely to proliferate.

In referring to these lesions, I have used both the common names, odontogenic keratocyst and 'primordial cyst'. Why 'primordial'? Because the keratocyst sometimes occurs in an area in which a tooth has failed to develop, it was supposed that the cyst resulted from a change in the primordium of the enamel organ. If we accept this hypothesis as invariable fact, then we are uncomfortable when faced with the observation that many keratocysts develop in an area with no missing teeth. To make the situation more comfortable, we now postulate that, in those cases, the keratocyst developed from the primordium of a supernumerary tooth – and conversely we explain the absence of the supposed supernumerary by saying that the 'primordial' cyst developed in its place. For my own part, I would be content to postulate that the odontogenic keratocyst can develop from various parts of the odontogenic epithelium, without requiring the involvement of an enamel organ. I suspect that this primordial Emperor has no clothes.

Giant Cell Lesions

Giant cell lesions of bone exert a peculiar fascination: they fascinate clinicians, radiologists, pathologists, and examiners. All these groups are concerned with the problems of differential diagnosis: pathologists are intrigued by the uncertainties regarding the origin and nature of the giant cells, and by their beauty as objects seen under the microscope: examiners have good reason to ask questions about giant cell lesions, because of the variety that occur in the jaws.

It has long been known that a giant cell tumour occurs in various parts of the skeleton and especially towards the ends of long bones. In 1953 Jaffe published a paper in which he crystallized the

growing realization that most of the intraosseous giant cell lesions of the jaws are not of the same character as giant cell tumours occurring in other bones.

For this relatively common lesion of the jaws, Jaffe proposed the name 'giant-cell reparative granuloma', and by choosing this name he indicated his opinion that the lesion is not a neoplasm. But why 'reparative' granuloma? Certainly new bone sometimes forms at the periphery of the lesion, and within the lesion itself. Certainly, too, the lesional tissue is richly vascular and fibroblastic – hence, presumably, the term granuloma. In fact, the structure of the lesional tissue is indistinguishable from that of a brown node of hyperparathyroidism, and I cannot recall hearing anyone refer to that as a reparative lesion. Jaffe himself acknowledged that he did not know what the giant cell reparative granuloma was repairing, and it seems to many of us that the time has come to modify the name, by omitting 'reparative'. This behaves as an innocent but slowly destructive lesion. It seems to be peculiar to the jaws, having no exact counterpart elsewhere in the skeleton. Why should this be, and why is the giant cell granuloma confined to the tooth-bearing areas? In cherubism, which is also an innocent giant cell lesion, the ramus is commonly involved. Whilst discussing giant cell lesions, we should mention the giant cell epulis. This lesion too is confined to the tooth-bearing areas, but in this instance it is not commonly found further back in the mouth than the second premolar. In other words, it is usually found in those parts of the tooth-bearing area that carried the deciduous dentition. Why should this be? The deciduous teeth are resorbed by osteoclasts, but I find it difficult to believe that there is any special predisposition of those areas to form giant cells, just because giant cells were necessary for the resorption of the deciduous teeth. Yet this is what many students are still taught.

Let us for a moment exclude the giant cell epulis and consider other types, such as the fibrous epulis and its variants, and the granuloma pyogenicum (including the pregnancy granuloma).

Lee (1968) carried out a very detailed analysis of the clinical and histological findings in 416 patients with epulides that were not of the giant cell type. In 41 cases the records did not show the precise location of the lesion, and in the remaining 375 cases, 299 of the lesions were in the incisor, canine or premolar regions. Thus in this substantial series of patients with epulides that were not of the giant cell type, about 4 out of every 5 had the epulis in the part of the jaws that formerly carried the deciduous teeth. Very recently, Andersen *et al.* (1973) described a series of 97 patients with giant cell epulides, and of these 97 lesions, 20 were confined to the molar region. Thus, comparing this series of giant cell epulides with the series of other types of epulis described by Lee, the distribution of the lesions between the areas that carried the deciduous dentition and the areas that did not is the same. I wonder whether the giant cell epulis has a distribution which is significantly different from that of the other epulides.

Computer-aided Studies in Diagnostic Histopathology

One major area on which our successors may look back with interest is the area of diagnostic histopathology. At present, this is almost the only branch of pathology that remains subjective and nonquantitative. I believe that this situation will change, and must change if we are to make major advances.

As you may know, for several years we have been working on a series of computer-aided studies in histopathology, in an effort to enlist the help of the computer to improve our diagnostic methods (Kramer 1969, Kramer *et al.* 1970*a*, *b*, El-Labban *et al.* 1971). To mention our latest line of thought, the results of which will be published in detail elsewhere (Kramer *et al.* 1974), Fig 2 shows lichen planus, and any experienced pathologist would probably make that pro-

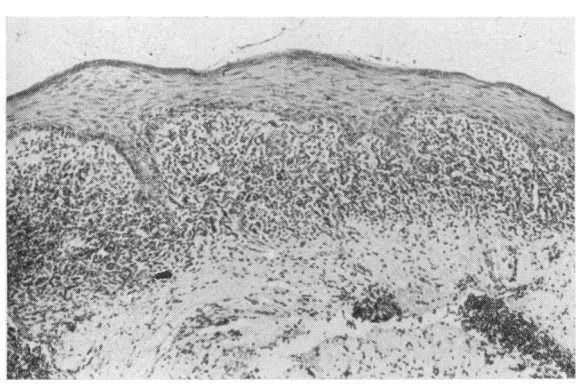

Fig 2 *Lichen planus of buccal mucosa*

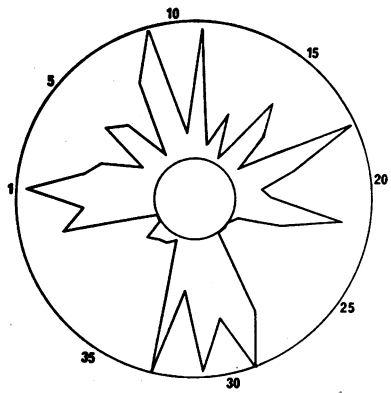

Fig 3 *Vector diagram showing, quantitatively, the typical histological features of a series of biopsies of oral lichen planus, based on 39 histological variables. The cases were selected by computer-aided cluster analysis, and the characteristics of the lichen planus cluster were calculated by further computer analysis*

visional diagnosis from this field; but he would do so subjectively, on the basis of experience, and he could not quantitate the reasons for his diagnosis or his degree of confidence in the diagnosis.

The polar vector diagram (Fig 3) shows, quantitatively, the histological characteristics of a group of lichen planus lesions. The lesions were identified and grouped by the computer, and the computer has calculated the importance of each tissue change that characterizes the group: the various tissue changes are numbered around the periphery of the graph. This polar graph is in effect the fingerprint of typical lichen planus. Similarly, we have calculated the fingerprints of certain other mucosal lesions and they are very different from one another. It is now possible for us to take an individual case, and calculate to which of these fingerprints it is most similar.

In preparation for this very brief review of some changing views, I read again a number of the books and journals published about twenty years ago. This exercise left me with a deep impression of how much has changed: of how much of what we accepted then is no longer acceptable: and often, of how naïve we were. At about the same time I found a very memorable sentence in a novel (Hartley 1953): 'The past is a foreign country: they do things differently there.' Perhaps it is as well to remember that our 'present' will be the past for our successors.

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